Bcl-2 Overexpression Improves Survival and Efficacy of Neural Stem Cell-Mediated Enzyme Prodrug Therapy.

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Public Summary:
Tumor-tropic neural stem cells (NSCs) can be engineered to localize gene therapies to invasive brain tumors. However, like other stem cell-based therapies, survival of therapeutic NSCs after transplantation is currently suboptimal. One approach to prolonging cell survival is to transiently overexpress an antiapoptotic protein within the cells prior to transplantation. Here, we investigate the utility and safety of this approach using a clinically tested, v-myc immortalized, human NSC line engineered to contain the suicide gene, cytosine deaminase (CD-NSCs). We demonstrate that both adenoviral- and minicircle-driven expression of the antiapoptotic protein Bcl-2 can partially rescue CD-NSCs from transplant-associated insults. We further demonstrate that the improved CD-NSC survival afforded by transient Bcl-2 overexpression results in decreased tumor burden in an orthotopic xenograft glioma mouse model following administrations of intracerebral CD-NSCs and systemic prodrug. Importantly, no evidence of CD-NSC transformation was observed upon transient overexpression of Bcl-2. This research highlights a critical need to develop clinically relevant strategies to improve survival of therapeutic stem cell posttransplantation. We demonstrate for the first time in this disease setting that improving CD-NSC survival using Bcl-2 overexpression can significantly improve therapeutic outcomes.

Scientific Abstract:
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